

EDITORIAL COMMENTS

RE: The tolerability of Potassium Citrate Tablet in patients with intolerance to Potassium Citrate Powder form

The authors have presented an interesting publication on the tolerability of tablet formulated potassium citrate in patients who were intolerant to the powder form of potassium citrate. They enrolled patients with calcium stones with hypocitraturia who were intolerant to the powder formulation of potassium citrate after one month of therapy into taking the tablet formulated form of potassium citrate for 2 weeks and concluded that the verbal taste scale of using tablets was significantly less than when they used the powder form. This is an important finding as one of the main problems with administration of potassium citrate is patients' low compliance with long term use of the medication as described earlier^(1,2). In one study, the long term compliance with only one evening dose of potassium citrate has been as low as 40%.

Nevertheless, the following points needs to be addressed:

The authors failed to provide a synchronous control sample. Ideally, they are expected to study the tolerance of the tablet and powder forms in two groups of patients with calcium stones with hypocitraturia and allocate them to treatment groups of tablet and powder preparations. Instead the intolerant patients to a medication were offered to a second medication. This trial design is famous in epidemiology and has previously been used for criticizing the studies on the influence of praise versus punishment on performance. The conclusion of these studies revealed that punishment influences more favorably than praising because participants after punishment acted better but participant who were gifted acted less favorably. The known error of these designs is "regression toward the mean" that is extreme tail of patients will naturally shift toward the mean value in the next measurements⁽³⁾. Then participant in the best performance tail who were gifted will naturally perform less favorably in their net measurement and participants in the least performance tail will naturally perform better in their next measurement. A similar problem has occurred with the study design of the authors as only intolerant patients to the powder form were enrolled, they are expected to report less intolerance if they were continued on the powder form for a longer duration.

A second point is tolerance to medication after continued use. Intolerance to some medications will mitigate after continual use. For example the side effects of tadalafil on muscle pain mitigates after continual use⁽⁴⁾. Therefore, less intolerance after continual use could be the influence of adaptation or not cannot be answered with the current trial design of the study.

And a last point is that the authors failed to report the adequacy of treatment on the powder formulation nor the tablet formulation based on urinary PH. Normally the amount of powder used daily is calibrated with urinary PH measurement. Improved responses were reported with urinary Ph > 6.5⁽⁵⁾. The average PH reported by the authors during trial is 6.1 with the standard deviation of .08 which indicates that a substantial number of participant could have urinary PH below 6.

In brief, in order to draw reliable conclusions, we need to wait for publication of randomized parallel group comparison of the tolerability of the powder and tablet formulations of potassium citrate as the authors have promised.

REFERENCES

1. Jendle-Bengtén C, Tiselius HG. Long-term follow-up of stone formers treated with a low dose of sodium potassium citrate. *Scand J Urol Nephrol*. 2000 ;34:36-41.
2. Pak CY, Fuller C, Sakhaee K, Preminger GM, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol*. 1985 ;134:11-9.
3. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol*. 2005; 34:215-20.
4. Hellstrom WJ. Current safety and tolerability issues in men with erectile dysfunction receiving PDE5 inhibitors. *Int J Clin Pract*. 2007 Sep;61(9):1547-54.
5. Robinson MR, Leita VA, Haleblan GE, Scales CD Jr, Chandrashekar A, Pierre SA, Preminger GM. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. *J Urol*. 2009 ;181:1145-50.

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I appreciate the editor's interest and comments on present article. The first point that the editor poses as the weakness of our study is a lack of a synchronous control group of calcium stones on powder form of potassium citrate. I disagree with this opinion, since the study design was according to quasi controlled trial, so the control group of our patients were themselves (before and after the taking drug).

The other point is mentioned about the short time of the study (two weeks) that how we could conclude the better tolerance to potassium citrate tablet versus powder form? Previous studies by Gonzalez et al.⁽¹⁾, Mechlin et al.⁽²⁾ have demonstrated the assessment of tolerance or the adverse effects of the potassium citrate preparations on upper gastro-intestinal mucosa can be even after three days of taking the medication. Of course it is acceptable that Intolerance to some medications will mitigate after long term consumption. Therefore, in confirmation with your opinion, another study with two parallel groups of calcium stone patients (Potassium citrate tablet and powder) is in processing, that the duration of treatment is longer and, the long term tolerance to potassium citrate preparations will be assessed.

Finally, the last point is regarding to the failure of potassium citrate tablet on urine pH correction. Although the changing of spot urine pH (5.7 ± 0.6 to 6.1 ± 0.8 , $p = 0.006$) and 24-hour urine citrate (235.8 ± 190.2 to 482.5 ± 323.2 , $p = 0.0002$) were significantly high after the treatment in our study⁽³⁾, it is noteworthy that the correction of these urine metabolites are of our main goals in another study with longer treatment duration which above mentioned.

REFERENCES

1. Gonzalez GB, Pak CY, Adams-Huet B, Taylor R, Bilhartz LE. Effect of potassium-magnesium citrate on upper gastrointestinal mucosa. *Alimentary pharmacology & therapeutics*. 1998;12(1):105-10.
2. Mechlin C, Kalorin C, Asplin J, White M. Splenda(R) improves tolerance of oral potassium citrate supplementation for prevention of stone formation: results of a randomized double-blind trial. *Journal of endourology / Endourological Society*. 2011;25(9):1541-5.
3. Basiri A, Taheri F, Taheri M. The tolerability of Potassium Citrate Tablet in patients with intolerance to Potassium Citrate Powder form. *Urology journal*. 2018;15(1):16-20.

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